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(54) CERTAIN 1,4,5-TRI-SUBSTITUTED IMIDAZOLE COMPOUNDS USEFUL AS CYTOKINE

BESTIMMTE 1,4,5-TRISUBSTITUIERTE IMIDAZOLEVERBINDUNGEN ZUR VERWENDUNG ALS CYTOKIN

CERTAINS COMPOSES D'IMIDAZOLE 1,4,5-TRISUBSTITUES UTILES COMME CYTOKINE

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- **GALLAGHER T F ET AL: "2,4,5-TRIARULIMIDAZOLE INHIBITORS OF IL-1 BIOSYNTHESIS" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 5, no. 11, 1 January 1995, pages 1171-1176, XP000568393**
- **CHEMICAL ABSTRACTS, Volume 93, No. 7, issued 18 August 1980, CAWKILL et al., "The Reaction Between Cyanide Ion and Nitrones; A New Imidazole Synthesis", Abstract No. 93:71635s; & J. CHEM. SOC., PERKIN TRANS. 1, 1980, (1), pages 244-248.**
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The file contains technical information submitted after the application was filed and not included in this specification

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Description

[0001] This invention relates to a novel compound, 5-(4-pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole, processes for the preparation thereof, the use thereof in treating cytokine mediated diseases and pharmaceutical compositions for use in such therapy.

BACKGROUND OF THE INVENTION

[0002] Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are biological substances produced by a variety of cells, such as monocytes or macrophages. IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

[0003] There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cells.

[0004] Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985), reviews the biological activities which have been attributed to IL-1. It should be noted that some of these effects have been described by others as indirect effects of IL-1.

[0005] Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

[0006] AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T Cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Monokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by inhibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T-cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, et al., Proc. Natl. Acad. Sci., 87: 782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells.

[0007] TNF has also been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, and the herpes virus for similar reasons as those noted.

[0008] Interleukin-8 (IL-8) is a chemotactic factor first identified and characterized in 1987. IL-8 is produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, and keratinocytes. Its production from endothelial cells is induced by IL-1, TNF, or lipopolysachharide (LPS). Human IL-8 has been shown to act on Mouse, Guinea Pig, Rat, and Rabbit Neutrophils. Many different names have been applied to IL-8, such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor.

[0009] IL-8 stimulates a number of functions in vitro. It has been shown to have chemoattractant properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and

atopic individuals as well as lysozomal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis, this may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many diseases are characterized by massive neutrophil infiltration. Conditions associated with an increased in IL-8 production (which is responsible for chemotaxis of neutrophil into the inflammatory site) would benefit by compounds which are suppressive of IL-8 production.

[0010] IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

[0011] There remains a need for treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs, i.e. compounds which are capable of inhibiting cytokines, such as IL-1, IL-6, IL-8 and TNF.

[0012] SUMMARY OF THE INVENTIONThe present invention relates to a novel compound, 5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole, or a pharmaceutically acceptable salt thereof.

[0013] This invention also relates to a pharmaceutical composition comprising 5-(4-pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole, or a pharmaceutically acceptable. salt thereof, and a pharmaceutically acceptable carrier or diluent.

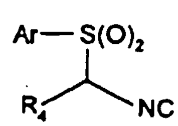
[0014] Another aspect of the invention is the use of 5-(4-pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating inflammation.

[0015] A further aspect of the invention is the use of 5-(4-pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a CSBP/RK/p38 kinase mediated disease.

[0016] Accordingly, this invention also relates to the use of 5-(4-pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a CSBP/RK/p38 kinase mediated disease, in which the CSBP/RK/p38 kinase mediated disease is selected from the group consisting of:

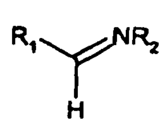
a) rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, acute synovitis, gouty arthritis and other arthritic conditions;
b) sepsis, septic shock, endotoxic shock, gram negative sepsis and toxic shock syndrome;
c) asthma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis and pulmonary sarcososis;
d) bone resorption diseases, osteoporosis, graft vs. host reaction, allograft rejections and pyresis;
e) stroke, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis and cerebral malaria;
f) diabetes and pancreatic β-cells;
g) multiple sclerosis and muscle degeneration;
h) atherosclerosis and Alzheimer's disease;
i) eczema, psoriasis, sunburn and conjunctivitis; and
j) Crohn's disease, ulcerative colitis and inflammatory bowel disease.

[0017] Another aspect of the invention is a process for the production of 5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole, which comprises reacting a compound of formula (IIa):



(IIa)

with a compound of formula (III):



(III)

and a base strong enough to deprotonate the isonitrile moiety of formula (IIa); and wherein the imine of formula (III) is formed in situ prior to reaction with the compound of formula (IIa); R_1 is 4-pyridyl or a precursor thereof, R_2 is 4-piperidinyl or a precursor thereof, R_4 is 4-fluorophenyl or a precursor thereof, and Ar is an optionally substituted phenyl group, and thereafter if necessary, converting a precursor of R_1, R_2 or R_4 to a group R_1, R_2 or R_4.

[0018] Another aspect of the invention is the above-described process, wherein the base is an amine, an amide, a carbonate, a hydride, or an alkyl or aryl lithium reagent or a mono-, di- or tribasic phosphate.

[0019] The present invention also relates to the above-described process, wherein the imine is formed in situ: a) by reacting an aldehyde of the formula R_1CHO, wherein R_1 is 4-pyridyl, with a primary amine of formula R_2NH_2 wherein R_2 is 1-t-butoxycarbonyl-4-piperidinyl or 4-piperidinyl and R_2 may be suitably protected as necessary and also wherein formation of the imine in situ utilises dehydrating conditions.

[0020] Another aspect of the invention is the above-described process which is further performed in a solvent selected from N,N-dimethylformamide (DMF), a halogenated solvent, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), an alcohol, benzene, toluene, and DME.

[0021] The invention also relates to the above-described process wherein:

a) the aldehyde of formula R_1CHO is formed in situ, or
b) the aldehyde is formed by the hydrolysis of an acetal of the formula $R_1CH(OR_a)_2$

wherein R_1 is 4-pyridyl or a precursor thereof, and R_a is C_{1-6}alkyl, aryl, aryl C_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl.

[0022] The present invention also provides the following compounds:

5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(1-t-butoxycarbonyl-4-piperidinyl)imidazole, or a pharmaceutically acceptable salt thereof.

5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(1-t-butoxycarbonyl-4-piperidinyl)imidazole

5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole

and a pharmaceutical composition comprising 5-(4-pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole and a pharmaceutically acceptable carrier or diluent.

[0023] This invention relates to the novel compounds of Formula (I) and pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable diluent or carrier.

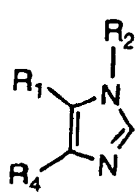
[0024] This invention also relates to a method of inhibiting cytokines and the treatment of a cytokine mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I)

[0025] This invention more specifically relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I)

[0026] This invention more specifically relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I)

[0027] This invention more specifically relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

[0028] Accordingly, the present invention provides a compound of Formula (I):



(I)

R1 is 4-pyridyl;
R4 is 4-fluorophenyl;
R2 is piperidinyl;
or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0029] The novel compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than humans, in need of inhibition of cytokine inhibition or production. In particular, cytokine mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted herein in the Methods of Treatment section, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retrovirus infections, such as but not limited to feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

[0030] Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

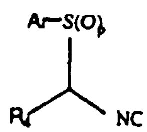
[0031] The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

[0032] The present invention includes novel species as exemplified below:

5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl) imidazole;
5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(1-t-butoxy carbonyl-4-piperidinyl) imidazole.

[0033] In a further aspect the present invention provides for the synthesis of compounds of Formula (I) as illustrated above.

[0034] Also described herein are compounds of the Formula (IIa) having the structure:

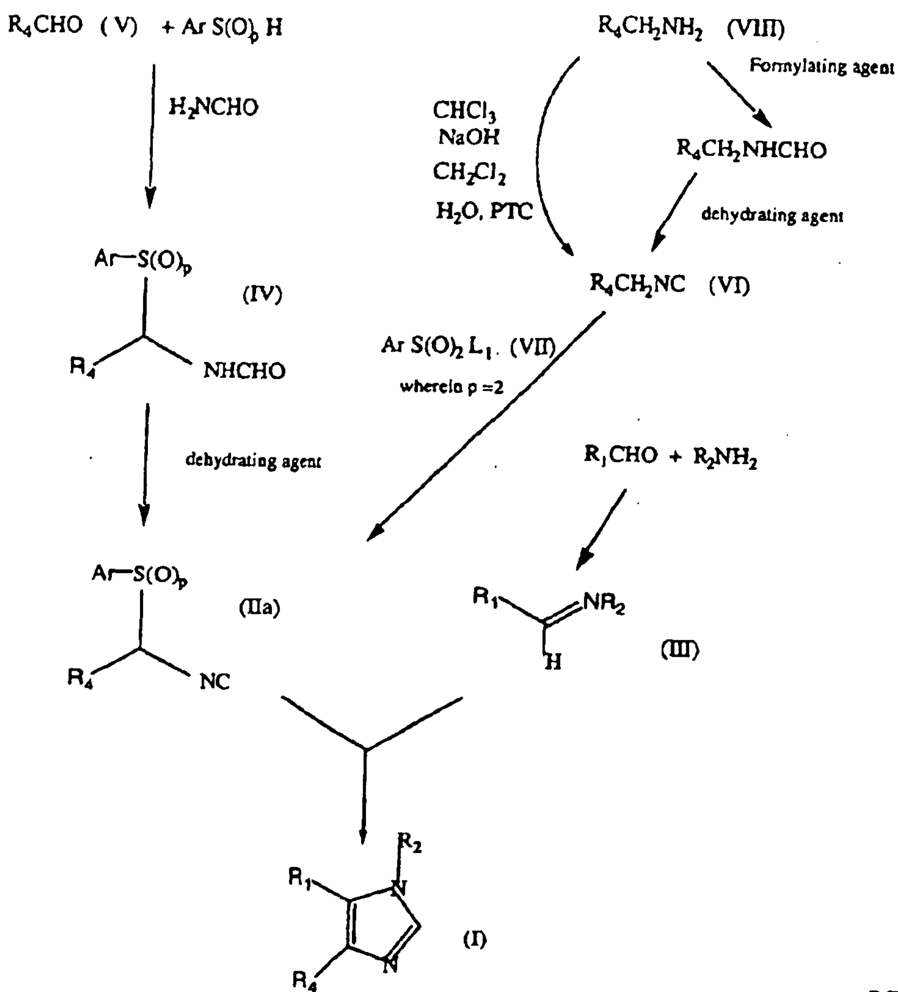


(IIa)

wherein p is 0, or 2; R4 is as defined for Formula (I) and Ar is an optionally substituted aryl as defined herein. Suitably, Ar is phenyl optionally substituted by C1-4alkyl, C1-4 alkoxy or halo. Preferably Ar is phenyl or 4-methylphenyl, i.e. a tosyl derivative.

[0035] The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in Schemes I to XI herein. The synthesis provided for in these Schemes is applicable for the producing compounds of Formula (I) having a variety of different R1, R2, and R4 groups which are reacted, employing optional substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. Once the imidazole nucleus has been established, further compounds of Formula (I) may be prepared by applying standard techniques for functional group interconversion, well known in the art.

[0036] Precursors of the groups R1, R2 and R4 are groups which can be interconverted by applying standard techniques for functional group inter-conversion.



SCHEME I

[0037] Referring to Scheme I the compounds of Formula (I) are suitably prepared by reacting a compound of the Formula (IIa) with a compound of the Formula (III) wherein p is 0 or 2, R1, R2 and R4 are as defined herein, for Formula (I), or are precursors of the groups R1, R2 and R4, and Ar is an optionally substituted phenyl group, and thereafter if necessary converting a precursor of R1, R2 and R4 to a group R1, R2 and R4. It is recognized that R2NH2 which is reacted with R1CHO to form the imine, Formula (III) the R2 moiety when it contains a reactive functional group, such as a primary or secondary amine, an alcohol, or thiol compound the group must be suitably protected. Suitable protecting groups may be found in, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981, whose disclosure is incorporated herein by reference. For instance, when R2 is a heterocyclic ring, such as a piperidine ring, the nitrogen is protected with groups such as t-Boc, CO2R18, or a substitued arylalkyl moiety.

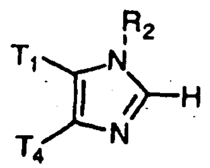
[0038] Suitably, the reaction is performed at ambient temperature or with cooling (e.g. -50° to 10°) or heating in an inert solvent such as methylene chloride, DMF, tetrahydrofuran, toluene, acetonitrile, or dimethoxyethane in the presence of an appropriate base such as K2CO3, t-buNH2, 1,8-diazabicyclo [5.4.0.] undec-7-ene (DBU), or a guanidine base such as 1,5,7-triazabicyclo [4.4.0] dec-5-ene (TBD). The intermediates of formula (II) have been found to be very stable and capable of storage for a long time. Preferably, p is 2.

[0039] Reaction a compound of the Formula (IIa) wherein p = 2, with a compound of the Formula (III)-Scheme I gives consistently higher yields of compounds of Formula (I) than when p=0. In addition, the reaction of Formula (IIa) compounds wherein p = 2 is more environmentally and economically attractive. When p=0, the preferred solvent used is methylene chloride, which is environmentally unattractive for large scale processing, and the preferred base, TBD, is also expensive, and produces some byproducts and impurities, than when using the commercially attractive synthesis (p=2) as further described herein.

[0040] As noted, Scheme I utilizes the 1,3-dipolar cycloadditions of an anion of a substituted aryl thiomethylisocyanide

(when p=0) to an imine. More specifically, this reaction requires a strong base, such as an amine base, to be used for the deprotonation step. The commercially available TBD is preferred although t-butoxide, Li+ or Na+, or K+ hexamethyldisilazide may also be used. While methylene chloride is the prefered solvent, other halogenated solvents, such as chloroform or carbon tetrachloride; ethers, such as THF, DME, DMF, diethylether, t-butyl methyl ether; as well as acetonitrile, toluene or mixtures thereof can be utiltized. The reaction may take place from about -20°C to about 40°C, preferably from about 0°C to about 23°C, more preferably from about 0°C to about 10°C, and most preferably about 4°C for reactions involving an R1 group of pyrimidine. For compounds wherein R1 is pyridine, it is recognized that varying the reations conditions of both temperature and solvent may be necessary, such as decreasing temperatures to about -50°C or changing the solvent to THF.

[0041] In a further process, compounds of Formula (I) may be prepared by coupling a suitable derivative of a compound of Formula (IX):



(IX)

wherein T1 is hydrogen and T4 is R4 , or alternatively T1 is R1 and T4 is H in which R1, R2 and R4 are as hereinbefore defined; with: (i) when T1 is hydrogen, a suitable derivative of the heteroaryl ring R1H, under ring coupling conditions, to effect coupling of the heteroaryl ring R1 to the imidazole nucleus at position 5; (ii) when T4 is hydrogen, a suitable derivative of the aryl ring R4H, under ring coupling conditions, to effect coupling of the aryl ring R4 to the imidazole nucleus at position 4.

[0042] Such aryl/heteroaryl coupling reactions are well known to those skilled in the art. In general, an organometallic synthetic equivalent of an anion of one component is coupled with a reactive derivative of the second component, in the presence of a suitable catalyst. The anion equivalent may be formed from either the imidazole of Formula (IX), in which case the aryl/heteroaryl compound provides the reactive derivative, or the aryl/heteroaryl compound in which case the imidazole provides the reactive derivative. Accordingly, suitable derivatives of the compound of Formula (IX) or the aryl/heteroaryl rings include organometallic derivatives such as organomagnesium, organozinc, organostannane and boronic acid derivatives and suitable reactive derivatives include the bromo, iodo, fluorosulfonate and trifluoromethanesulphonate derivatives. Suitable procedures are described in WO 91/19497, the disclosure of which is incorporated by reference herein.

[0043] Suitable organomagnesium and organozinc derivatives of a compound of Formula (IX) may be reacted with a halogen, fluorosulfonate or triflate derivative of the heteroaryl or aryl ring, in the presence of a ring coupling catalyst, such as a palladium (O) or palladium (II) catalyst, following the procedure of Kumada *et al.*, Tetrahedron Letters, **22**, 5319 (1981). Suitable such catalysts include *tetrakis*-(triphenylphosphine)palladium and PdCl2[1,4-*bis*-(diphenylphosphino)-butane], optionally in the presence of lithium chloride and a base, such as triethylamine. In addition, a nickel (II) catalyst, such as Ni(II)Cl2(1,2-biphenylphosphino)ethane, may also be used for coupling an aryl ring, following the procedure of Pridgen et al., J. Org. Chem, 1982, **47**, 4319. Suitable reaction solvents include hexamethylphosphoramide. When the heteroaryl ring is 4-pyridyl, suitable derivatives include 4-bromo- and 4-iodo-pyridine and the fluorosulfonate and inflate esters of 4-hydroxy pyridine. Similarly, suitable derivatives for when the aryl ring is phenyl include the bromo, fluorosulfonate, triflate and, preferably, the iodo-derivatives. Suitable organomagnesium and organozinc derivatives may be obtained by treating a compound of Formula (IX) or the bromo derivative thereof with an alkyllithium compound to yield the corresponding lithium reagent by deprotonation or transmetallation, respectively. This lithium intermediate may then be treated with an excess of a magnesium halide or zinc halide to yield the corresponding organometallic reagent.

[0044] A trialkyltin derivative of the compound of Formula (IX) may be treated with a bromide, fluorosulfonate, triflate, or, preferably, iodide derivative of an aryl or heteroaryl ring compound, in an inert solvent such as tetrahydrofuran, preferably containing 10% hexamethylphosphoramide, in the presence of a suitable coupling catalyst, such as a palladium (0) catalyst, for instance *tetrakis*-(triphenylphosphine)-palladium, by the method described in by Stille, J. Amer. Chem. Soc, 1987, **109**, 5478, US Patents 4,719,218 and 5,002,942, or by using a palladium (II) catalyst in the presence of lithium chloride optionally with an added base such as triethylamine, in an inert solvent such as dimethyl formamide. Trialkyltin derivatives may be conveniently obtained by metallation of the corresponding compound of Formula (IX) with a lithiating agent, such as *s*-butyl-lithium or *n*-butyllithium, in an ethereal solvent, such as tetrahydrofuran, or treatment of the bromo derivative of the corresponding compound of Formula (IX) with an alkyl lithium, followed, in

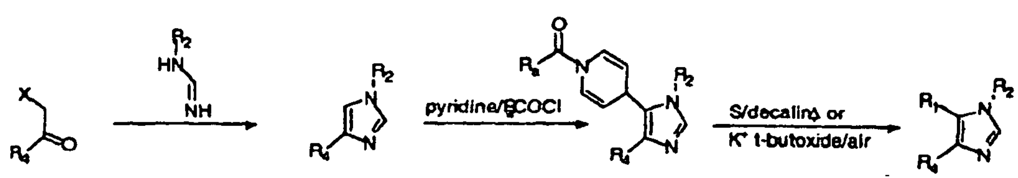
each case, by treatment with a trialkyltin halide. Alternatively, the bromo- derivative of a compound of Formula (IX) may be treated with a suitable heteroaryl or aryl trialkyl tin compound in the presence of a catalyst such as *tetrakis*-(triphenyl-phosphine)-palladium, under conditions similar to those described above.

[0045] Boronic acid derivatives are also useful. Hence, a suitable derivative of a compound of Formula (IX), such as the bromo, iodo, triflate or fluorosulphonate derivative, may be reacted with a heteroaryl- or aryl-boronic acid, in the presence of a palladium catalyst such as *tetrakis*-(triphenylphosphine)-palladium or PdCl2[1,4-*bis*-(diphenyl-phosphino)-butane] in the presence of a base such as sodium bicarbonate, under reflux conditions, in a solvent such as dimethoxyethane (see Fischer and Haviniga, Rec. Trav. Chim. Pays Bas, **84**, 439, 1965, Snieckus, V., Tetrahedron Lett., **29**, 2135,1988 and Terashimia, M., Chem. Pharm. Bull., **11**, 4755, 1985). Non-aqueous conditions, for instance, a solvent such as DMF, at a temperature of about 100°C, in the presence of a Pd(II) catalyst may also be employed (see Thompson W J *et al*, J Org Chem, **49**, 5237, 1984). Suitable boronic acid derivatives may be prepared by treating the magnesium or lithium derivative with a trialkylborate ester, such as triethyl, tri-*iso*-propyl or tributylborate, according to standard procedures.

[0046] In such coupling reactions, it will be readily appreciated that due regard must be exercised with respect to functional groups present in the compounds of Formula (IX). Thus, in general, amino and sulfur substituents should be non-oxidised or protected.

[0047] Compounds of Formula (IX) are imidazoles and may be obtained by any of the procedures herein before described for preparing compounds of Formula (I). In particular, an α-halo-ketone or other suitably activated ketones R4COCH2Hal (for compounds of Formula (IX) in which T1 is hydrogen) or R1COCH2Hal (for compounds of Formula (IX) in which T4 is hydrogen) may be reacted with an amidine of the formula R2NH-C=NH, wherein R2 is as defined in Formula (I), or a salt thereof, in an inert solvent such as a halogenated hydrocarbon solvent, for instance chloroform, at a moderately elevated temperature, and, if necessary, in the presence of a suitable condensation agent such as a base. The preparation of suitable a-halo-ketones is described in WO 91/19497. Suitable reactive esters include esters of strong organic acids such as a lower alkane sulphonic or aryl sulphonic acid, for instance, methane or *p*-toluene sulphonic acid. The amidine is preferably used as the salt, suitably the hydrochloride salt, which may then be converted into the free amidine *in situ* , by employing a two phase system in which the reactive ester is in an inert organic solvent such as chloroform, and the salt is in an aqueous phase to which a solution of an aqueous base is slowly added, in dimolar amount, with vigorous stirring. Suitable amidines may be obtained by standard methods, see for instance, Garigipati R, Tetrahedron Letters, 190, **31**, 1989.

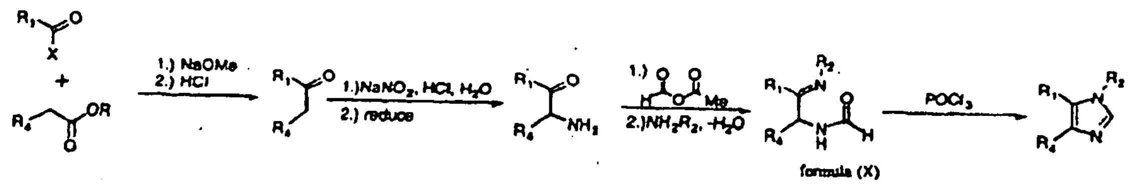
[0048] Compounds of Formula (I) may also be prepared by a process which comprises reacting a compound of Formula (IX), wherein T1 is hydrogen, with an **N**-acyl heteroaryl salt, according to the method disclosed in US patent 4,803,279, US patent 4,719,218 and US patent 5,002,942, to give an intermediate in which the heteroaryl ring is attached to the imidazole nucleus and is present as a 1,4-dihydro derivative thereof, which intermediate may then be subjected to oxidative-deacylation conditions (Scheme II). The heteroaryl salt, for instance a pyridinium salt, may be either preformed or, more preferably, prepared *in situ* by adding a substituted carbonyl halide (such as an acyl halide, an aroyl halide, an arylalkyl haloformate ester, or, preferably, an alkyl haloformate ester, such as acetyl bromide, benzoylchloride, benzyl chloroformate, or, preferably, ethyl chloroformate) to a solution of the compound of Formula (IX) in the heteroaryl compound R1H or in an inert solvent such as methylene chloride to which the heteroaryl compound has been added. Suitable deacylating and oxidising conditions are described in U.S. Patent Nos. 4,803,279, 4,719,218 and 5,002,942, which references are hereby incorporated by reference in their entirety. Suitable oxidizing systems include sulfur in an inert solvent or solvent mixture, such as decalin, decalin and diglyme, *p*-cymene, xylene or mesitylene, under reflux conditions, or, preferably, potassium *t*-butoxide in *t*-butanol with dry air or oxygen.



SCHEME II

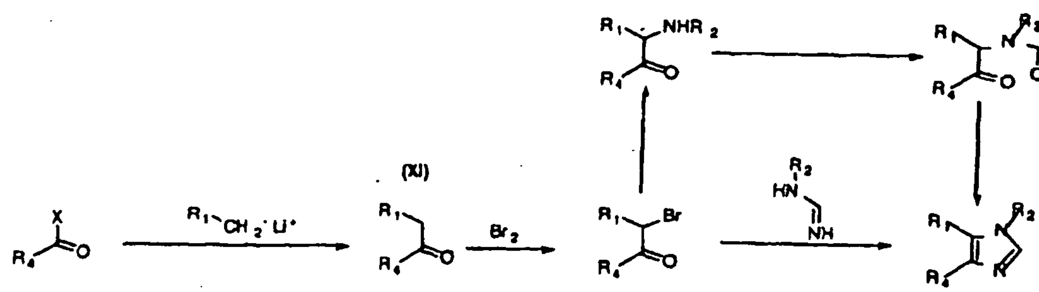
[0049] In a further process, illustrated in Scheme III below, compounds of Formula (I) may be prepared by treating a compound of Formula (X) thermally or with the aid of a cyclising agent such as phosphorus oxychloride or phosphorus pentachloride (see Engel and Steglich, Liebigs Ann Chem, 1978, 1916 and Strzybny *et al.*, J Org Chem, 1963, **28**, 3381). Compounds of Formula (X) may be obtained, for instance, by acylating the corresponding a-keto-amine with an activated formate derivative such as the corresponding anhydride, under standard acylating conditions followed by forma-

tion of the imine with R2NH2. The aminoketone may be derived from the parent ketone by oxamination and reduction and the requisite ketone may in turn be prepared by decarboxylation of the beta-ketoester obtained from the condensation of an aryl (heteroaryl) acetic ester with the R1COX component.



SCHEME III

[0050] In Scheme IV illustrated below, two (2) different routes which use ketone (formula XI) for preparing a compound of Formula (I). A heterocyclic ketone (XI) is prepared by adding the anion of the alkyl heterocycle such as 4-methylquinoline (prepared by treatment thereof with an alkyl lithium, such as *n*-butyl lithium) to an N-alkyl-O-alkoxybenzamide, ester, or any other suitably activated derivative of the same oxidation state. Alternatively, the anion may be condensed with a benzaldehyde, to give an alcohol which is then oxidised to the ketone (XI).



SCHEME IV

[0051] In a further process, N-substituted compounds of Formula (I) may be prepared by treating the anion of an amide of Formula (XII):

R1CH2NR2COH (XII)

wherein R1 and R2 with:

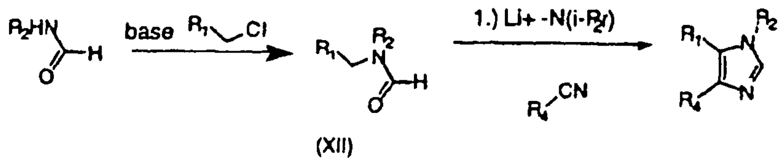
(a) a nitrile of the Formula (XIII):

R4CN (XIII)

wherein R4 is as hereinbefore defined, or
(b) an excess of an acyl halide, for instance an acyl chloride, of the Formula (XIV):

R4COHal (XIV)

wherein R4 is as hereinbefore defined and Hal is halogen, or a corresponding anhydride, to give a *bis*-acylated intermediate which is then treated with a source of ammonia, such as ammonium acetate.

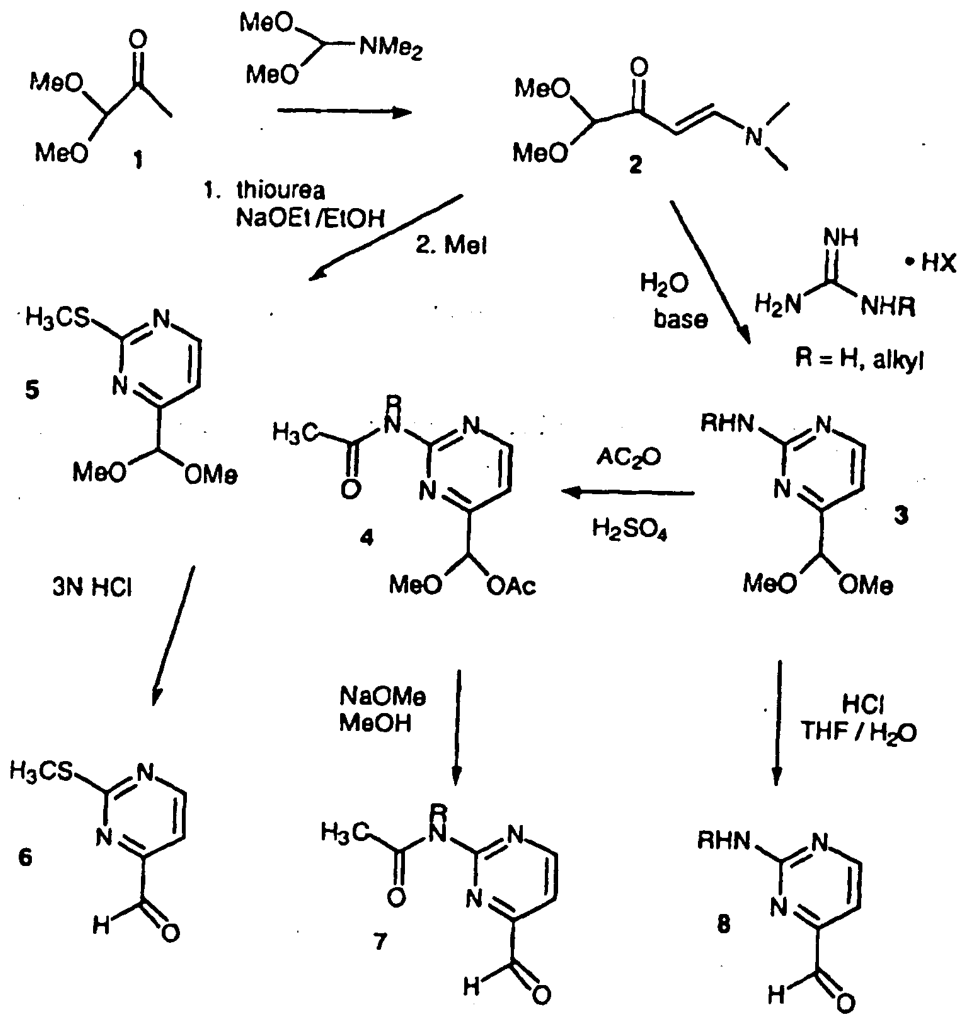


SCHEME V

[0052] One variation of this approach is illustrated in Scheme V above. A primary amine (R2NH2) is treated with a halomethyl heterocycle of Formula R1CH2X to give the secondary amine which is then converted to the amide by standard techniques. Alternatively the amide may be prepared as illustrated in scheme V by alkylation of the formamide with R1CH2X. Deprotonation of this amide with a strong amide base, such as lithium di-*iso*-propyl amide or sodium *bis*-(trimethylsilyl)amide, followed by addition of an excess of an aroyl chloride yields the *bis*-acylated compound which is then closed to an imidazole compound of Formula (I), by heating in acetic acid containing ammonium acetate. Alternatively, the anion of the amide may be reacted with a substituted aryl nitrile to produce the imidazole of Formula (I) directly.

[0053] The following description and schemes are further exemplification of the process as previously described above in Scheme I. Various pyrimidine aldehyde derivatives 6, 7 and 8 as depicted in scheme VI below, can be prepared by modification of the procedures of Bredereck et al. (*Chem. Ber.* **1964**, *97*, 3407) whose disclosure is incorporated by reference herein. These pyrimidine aldehydes are then utilized as intermediates in the synthesis as further described herein. The unprotected amino aldehyde derivative, e.g. 8, can be somewhat unstable. Use of an acetolysis procedure, as described in Scheme VI, wherein the aldehyde 7 is isolated as the acetamide derivative, (compound 3 is converted to 7, via the intermediate 4) and leads to a more stable compound for use in the cycloaddition reaction to make compounds of Formula (I).

[0054] General acetolysis conditions, for such a reaction are employed and are well known to those of skill in the art. Suitable conditions are exemplified, for instance in Example 83. In greater detail, the reaction employs heating the 2-amino pyrimidine dialkoxy acetal with acetic anhydride in the presence of a catalytic amount of concentrated sulfuric acid, which simultaneously acetylates the amine and leads to the exchange of one of the alkoxy groups for an acetoxy group. The resultant compound is converted to the aldehyde by deacetylation with a catalytic amount of an alkoxide salt and the corresponding alcohol solvent, e.g. Na+ methoxide and methanol. Alternatively, higher yields can be obtained by first acetylating the amine with acetic anhydride and then affecting exchange by subsequent addition of concentrated sulfuric acid.



Scheme VI

[0055] The reaction of imines with tosylmethyl isonitriles was first reported by van Leusen (van Leusen, et al., *J. Org. Chem.* **1977**, *42*, 1153.) Reported were the following conditions: tert butyl amine(tBuNH2) in dimethoxyethane (DME), K2CO3 in MeOH, and NaH in DME. Upon re-examination of these conditions each was found to produce low yields. The desired product for instance, 5-[(2-(1-methylamino)-pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole, was isolated at yields less than 50%, using t-BuNH2 in DME at room temperature, but a second pathway involving amine exchange to produce the t-butyl imine followed by reaction with the isocyanide **1** to produce the tBu imidazole was also operating. This will likely occur using any primary amine as a base. The secondary amines, while not preferred may be used, but may also decompose the isonitrile slowly. Reactions will likely require about 3 equivalents of amine to go to completion, resulting in approximately 50% isolated yields. Hindered secondary amines (diisopropylamine) while usable are very slow and generally not too effective. Use of tertiary and aromatic amines, such as pyridine, and triethyl-amine gave no reaction under certain test conditions, but more basic types such as DBU, and 4-dimethylamino pyridine (DMAP) while slow, did produce some yields and hence may be suitable for use herein.

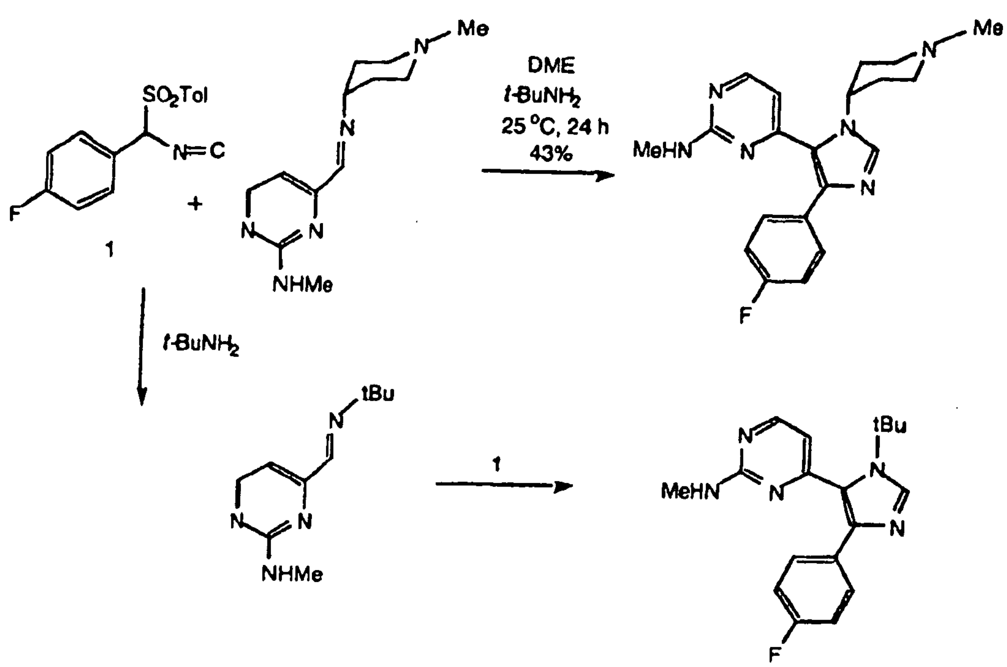
[0056] As depicted in Schemes VII and VIII below, the pyrimidine aldehydes of Scheme VI, can be condensed with a primary amine, to generate an imine, which may suitably be isolated or reacted in situ, with the desired isonitrile in the presence of a variety of suitable bases, and solvents as described herein to afford the 5-(4-pyrimidinyl)-imidazoles, wherein R2 and R4 are as defined herein for Formula (I) compounds.

[0057] One preferred method for preparing compounds of Formula (I) is shown below in Scheme VII. The imines, prepared and isolated in a separate step were often tars, which are hard to handle. The black color is also often carried over into the final product. The yield for making the imines varied, and environmentally less-acceptable solvents, such

as CH2Cl2 were often used in their preparation.

[0058] This reaction, wherein p=2, requires a suitable base for the reaction to proceed. The reaction requires a base strong enough to deprotonate the isonitrile. Suitable bases include an amine, a carbonate, a hydride, or an alkyl or aryl lithium reagent; or mixtures thereof. Bases include, but are not limited to, potassium carbonate, sodium carbonate, primary and secondary amines, such as t-butylamine, diisopropyl amine, morpholine, piperidine, pyrrolidine, and other non-nucleophilic bases, such as DBU, DMAP and 1,4-diazabicyclo[2.2.2]octane (DABCO).

[0059] Suitable solvents for use herein, include but are not limited to N,N-dimethyl-formamide (DMF), MeCN, halogenated solvents, such as methylene chloride or chloroform, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), alcohols, such as methanol or ethanol, benzene, toluene, DME, or EtOAc. Preferably the solvent is DMF, DME, THF, or MeCN, more preferably DMF. Product isolation may generally be accomplished by adding water and filtering the product as a clean compound.

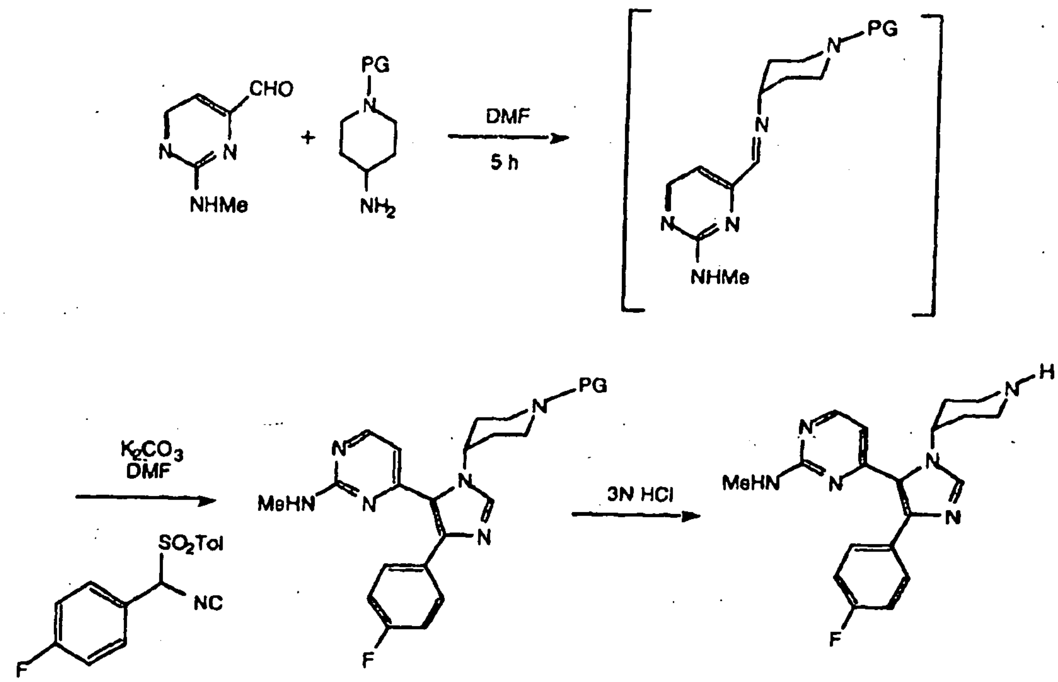


SCHEME VII

[0060] While not convenient for large scale work, addition of NaH, instead of t-butylamine, to the isonitrile, perhaps with temperatures lower than 25°C (in THF) are likely needed. Additionally, BuLi has also been reported to be an effective base for deprotonating tosyl benzylisonitriles at -50°C. (DiSanto, R.; Costi, R.; Massa, S.; Artico, M. *Synth. Commun.* **1995**, *25*, 795).

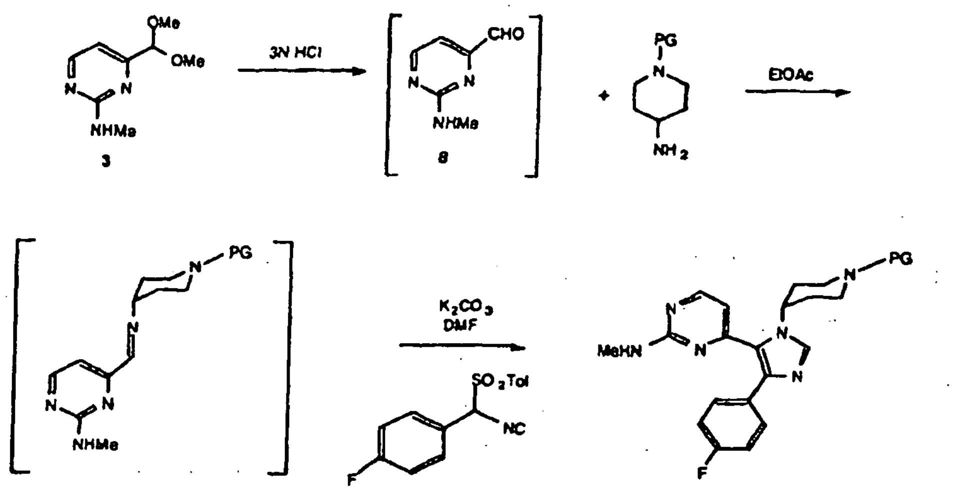
[0061] Various temperature conditions may be utilized depending upon the preferred base. For instance, using tBuNH2/DME and K2CO3/MeOH, reactions were tried at 0, room temperature, 40, about 64, and 80°C. At temperatures above 40°C, the yields may drop to about 20%, although not much difference has been seen between 0°C and room temperature. Using K2CO3 in DMF, reactions were tried at 0°C and 25°C, with virtually no difference in product, quality or yield. Consequently, temperature ranges below 0°C , and above 80°C are contemplated as also being within the scope of this invention. Preferably, the temperature ranges are from about 0°C to about 25°C. For purposes herein, room tempature, which is depicted as 25°C, but it is recognized that this may vary from 20°C to 30°C.

[0062] As shown in Scheme VIII below, the imine is preferably formed in situ in a solvent. This preferred synthesis, is a process which occurs as a one-pot synthesis. Suitably, when the primary amine is utilized as a salt, such as in the dihydrochloride salt in the Examples, the reaction may further include a base, such as potassium carbonate prior to the addition of the isonitrile. Alternatively, the piperidine nitrogen may be required to be protected (PG) as shown below, suitably the PG is BOC or C(O)2R, wherein R is preferably alkyl, aryl, arylalkyl moieties well known to those skilled in the art. Reaction conditions, such as solvents, bases, temperatures, etc. are similar to those illustrated and discussed above for the isolated imine as shown in Scheme VII. One skilled in the art would readily recognize that under some circumstances, the in situ formation of the imine may require dehydrating conditions, or may require acid catalysis.



SCHEME VIII

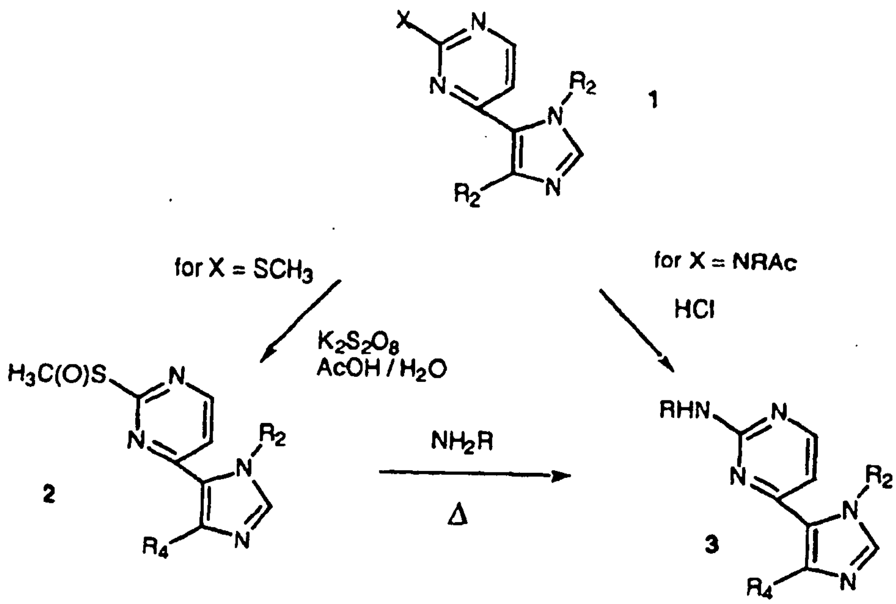
[0063] Another method for preparing compounds of Formula (I) is shown below in Scheme VIIIa. To avoid the difficulty associated with isolating the pyrimidine aldehyde 8, it is possible to hydrolyze the acetal 3 to aldehyde 8 as described in Example 378, part b. The aldehyde 8, formed in situ, can be treated sequentially with a primary amine, ethyl acetate, and NaHCO3 to form the corresponding imine in situ, which is extracted into the ethyl acetate. Addition of the isonitrile, a carbonate base and DMF allows for the formation of the 5-(4-pyrimidinyl)-imidazoles, wherein R2 and R4 are as defined herein for Formula (A) compounds.



SCHEME VIIIa

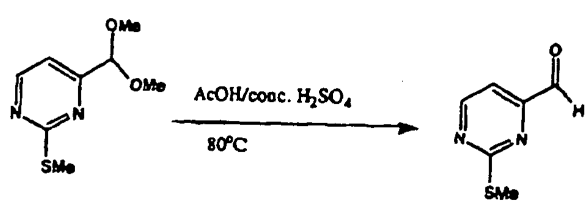
[0064] The preferred method of synthesis for compounds of Formula (I) also provides for a suitable and reliable method for introduction of an S(O)malkyl moiety on the pyrimidine (R1 group) by using, for instance, the 2-methylthio

pyrimidine aldehyde derivative, as is described in the Examples section. In scheme IX below, compound 1 (X = S methyl), while a final product may also be used as a precursor, as previously noted to make further compounds of formula (I). In this particular instance the methylthio moiety is oxidized to the methyl sulfinyl moiety which may additionally be further modified to a substituted amino group.



Scheme IX

[0065] Scheme X shows the novel hydrolysis of 2-thiomethyl-pyrimidine acetal to 2-thiomethylpyrimidine aldehyde. Hydrolysis of the acetal to aldehyde using various known reaction conditions, such as formic acid, did not produce a satisfactory yield of the aldehyde, <13% was obtained. One method of synthesis involves the use of AcOH (fresh) as solvent and con-centrated H2SO4 under heating conditions, preferably a catalytic amount of sulfuric acid. Heating conditions include temperatures from about 60° to 85°C, preferably from about 70° to about 80°C as higher temperatures show a darkening of the reaction mixture. After the reaction is completeed the mixture is cooled to about room temperature and the acetic acid is removed. A more preferred procedure involves heating the acetal in 3N HCL at 40°C for 18 hours, cooling and extracting the bicarbonate neutralized solution into EtOAc. Examples of these two procedures are described herein as Examples 6b and 25.



Scheme X

[0066] The compounds of Formula (I)can be prepared by one of three methods: 1) direct reaction of the 2-aminopyridine imine with the isonitrile; 2) condensation of the 2-acetamidopyridine imine with the isonitrile followed by removal of the acetamido group; and 3) oxidation of the 2-methylthiopyridine derivative to the corresponding sulfoxide followed by displacement with the desired amine.

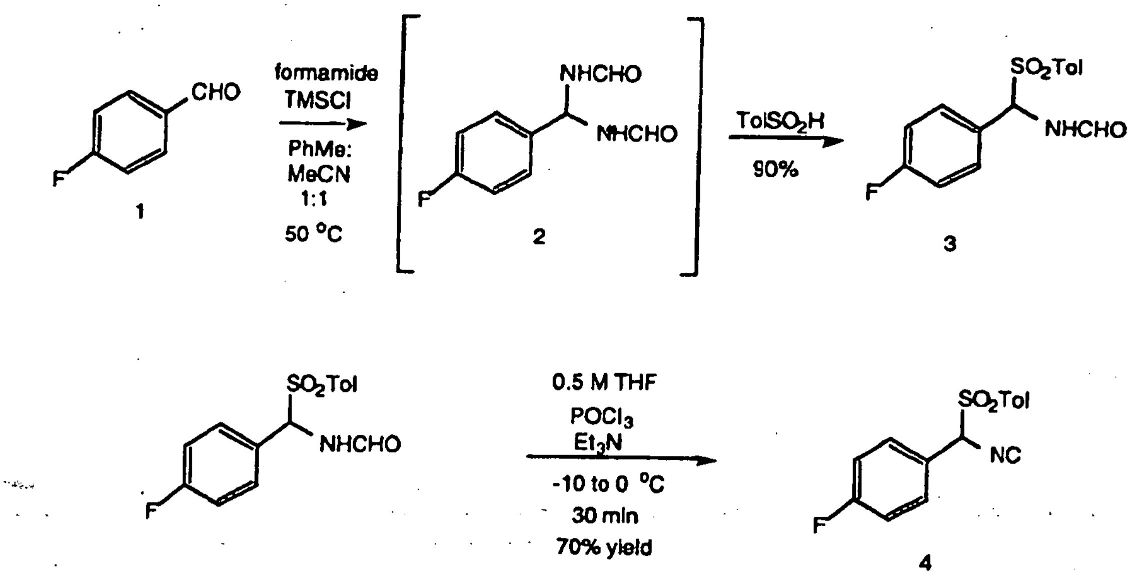
[0067] While these schemes herein are presented, for instance, with an optionally substituted piperidine moiety for the resultant R2 position, or a 4-fluoro phenyl for R4, any suitable R2 moiety or R4 moiety may be added in this manner if it can be prepared on the primary amine. Similarly, any suitable R4 can be added via the isonitrile route.

[0068] The compounds of Formula (IIa), in Scheme I, may be prepared by the methods of van Leusen et al., supra. For example a compound of the Formula (IIa) may be prepared by dehydrating a compound of the Formula (IV)-Scheme I, wherein Ar, R4 and p are as defined herein.

[0069] Suitable dehydrating agents include phosphorus oxychloride, oxalyl chloride, thionyl chloride, phosgene, or tosyl chloride in the presence of a suitable base such as triethylamine or diisopropylethylamine, or similar bases, etc. such as pyridine. Suitable solvents are dimethoxy ether, tetrahydrofuran, or halogenated solvents, preferably THF. The reaction is most efficent when the reaction temperatures are kept between -10°C and 0°C. At lower temperatures incomplete reaction occurs and at higher temperatures, the solution turns dark and the product yield drops.

[0070] The compounds of formula (IV)-Scheme I may be prepared by reacting a compound of the formula (V)-Scheme I, R4CHO where R4 is as defined herein, with ArS(0)pH and formamide with or without water removal, preferably under dehydrating conditions, at ambient or elevated temperature e.g. 30° to 150°, conveniently at reflux, optionally in the presence of an acid catalyst. Alternatively trimethysilylchloride can be used in place of the acid catalyst. Examples of acid catalysts include camphor-10-sulphonic acid, formic acid, p-toluenesulphonic acid, hydrogen chloride or sulphuric acid.

[0071] An optimal method of making an isonitrile of Formula (IIa) is illustrated below, in Scheme XI, and in the Examples section, Example 10 herein.



SCHEME XI

[0072] The conversion of the substituted aldehyde to the tosylbenzyl formamide may be accomplished by heating the aldehyde, 1-Scheme XI, with an acid, such as p-toluene-sulfonic acid, formic acid or camphorsulfonic acid; with formamide and p-toluene-sulfinic acid [under reaction conditions of about 60°C for about 24 hours]. Preferably, no solvent is used. The reaction, may give poor yields (< 30%) when solvents, such as DMF, DMSO, toluene, acetonitrile, or excess formamide are used. Temperatures less than 60°C are generally poor at producing the desired product, and temperatures in excess of 60°C may produce a product which decomposes, or obtain a benzylic bis-formamide 2-Scheme XI. In Example 23 (a), described in WO 95/02591, Adams et al., synthesizes 4-Fluorophenyl-tosylmethylformamide, a compound of Formula (IV) -Scheme I, wherein p = 2. This procedure differs from that presently described herein in Example 10 by the following conditions, using the sodium salt of toluene sulfinic acid, neat which process results in uneven heating, lower yields and lower reproduceability then the present invention, as described herein which uses sulfinic acid and allows for use of non-aqueous conditions.

[0073] Conditions for making α-(p-Toluenesulfonyl)-4-fluorobenzylisonitrileas described in Example 23 (b), of WO 95/02591, Adams et al., used as a solvent MeCl to extract the product and DME as solvent. The present invention improves upon this process by utiizing less expensive solvents, such as THF and EtOAc to extract. Further higher yields are obtained by recrystalizing with an alcohol, such as 1-propanol, although other alcohols, such as methanol, ethanol and butanols are acceptable. Previously, the compound was partially purifed using chromatography techniques, and hazardous solvents for additional purifications.

[0074] Also described herein is the synthesis of the tosyl benzyl formamide compound, achieved by reacting the bisformamide intermediate 2- Scheme XI with p-toluenesulfinic acid. In this preferred route, preparation of the bis-

formamide from the aldehyde is accomplished by heating the aldehyde with formamide, in a suitable solvent with acid catalysis. Suitable solvents are toluene, acetonitrile, DMF, and DMSO or mixtures thereof. Acid catalysts, are those well known in the art, and include but are not limited to hydrogen chloride, p-toluenesulfonic acid, camphorsulfonic acid, and other anhydrous acids. The reaction can be conducted at temperatures ranging from about 25°C to 110°C, preferably about 50°C, suitably for about 4 to about 5 hours, longer reaction times are also acceptable. Product decomposition and lower yields may be observed at higher temperatures (>70°C) at prolonged reactions times. Complete conversion of the product generally requires water removal from the reaction mixture.

[0075] Preferred conditions for converting a bis-formamide derivative to the tosyl benzyl formamide are accomplished by heating the bisformamide in a suitable solvent with an acid catalyst and p-toluenesulfinic acid. Solvents for use in this reaction include but are not limited to toluene, and acetonitrile or mixtures thereof. Additional mixtures of these solvents with DMF, or DMSO may also be used but may result in lower yields. Temperatures may range from about 30°C to about 100°C. Temperatures lower than 40°C and higher than 60°C are not preferred as the yield and rate decreases. Preferably the range is from about 40° to 60°C, most preferably about 50°C. The optimal time is about 4 to 5 hours, although it may be longer. Preferably, acids used include but are not limited to, toluenesulfonic acid, camphorsulfonic acid, and hydrogen chloride and other anhydrous acids. Most preferably the bisformamide is heated in toluene:acetonitrile in a 1:1 ratio, with p-toluenesulfinic acid and hydrogen chloride.

[0076] Also described herein is the preferred synthetic route for synthesis of the tosylbenzyl formamide compound which is accomplished using a one-pot procedure. This process first converts the aldehyde to the bis-formamide derivative and subsequently reacts the bis-formamide derivative with toluenesulfinic acid. This procedure combines the optimized conditions into a single, efficient process. High yields, >90% of the aryl (tosyl) benzylformamide may be obtained in such a manner.

[0077] Preferred reaction conditions employ a catalyst, such as trimethylsilyl chloride (TMSCl), in a preferred solvent, toluene:acetonitrile, preferably in a 1:1 ratio. A reagent, such as TMSCl , is preferred which reacts with water produced therein and at the same time produces hydrogen chloride to catalyze the reaction. Also preferred is use of hydrogen chloride and p-toluenesulfonic acid. Therefore, three suitable reaction conditions for use herein include 1) use of a dehydrating agent which also provides hydrogen chloride, such as TMSCl or p-toluene sulfinic acid; or by 2) use of a suitable dehydrating agent and a suitable source of acid source, such as but not limited to, camphorsulfonic acid, hydrogen chloride or p-toluenesulfonic acid; and 3) alternative dehydrating conditions, such as the azeotropic removal of water, and using an acid catalyst and p-toluene sulfinic acid.

[0078] Compounds of the formula (IIa) where p is 2 may also be prepared by reacting in the presence of a strong base a compound of the formula (VI) -Scheme I, R4CH2NC with a compound of the formula (VII)-Scheme I, ArSO2L1 wherein R4 and Ar are as defined herein and L1 is a leaving group such as halo, e.g. fluoro. Suitable strong bases include, but are not limited to, alkyl lithiums such as butyl lithium or lithium diisopropylamide (Van Leusen et al., Tetrahedron Letters, No. 23, 2367-68 (1972)).

[0079] The compounds of formula (VI)-Scheme I may be prepared by reacting a compound of the formula (VIII) -Scheme I, R4CH2NH2 with an alkyl formate (e.g. ethylformate) to yield an intermediate amide which can be converted to the desired isonitrile by reacting with well known dehydrating agent, such as but not limited to oxalyl chloride, phosphorus oxychloride or tosyl chloride in the presence of a suitable base such as triethylamine.

[0080] Alternatively a compound of the formula (VIII) - Scheme I may be converted to a compound of the formula (VI)- Scheme I by reaction with chloroform and sodium hydroxide in aqueous dichloromethane under phase transfer catalysis.

[0081] The compounds of the formula (III) - Scheme I may be prepared by reacting a compound of the formula R1CHO with a primary amine R2NH2.

[0082] The amino compounds of the formula (VIII) - Scheme I are known or can be prepared from the corresponding alcohols, oximes or amides using standard functional group interconversions.

[0083] Suitable protecting groups for use with hydroxyl groups and the imidazole nitrogen are well known in the art and described in many references, for instance, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981. Suitable examples of hydroxyl protecting groups include silyl ethers, such as t-butyldimethyl or t-butyldiphenyl, and alkyl ethers, such as methyl connected by an alkyl chain of variable link, (CR10R20)n. Suitable examples of imidazole nitrogen protecting groups include tetrahydropyranyl.

[0084] Pharmaceutically acid addition salts of compounds of Formula (I) may be obtained in known manner, for example, by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

METHODS OF TREATMENT

[0085] The compounds of Formula (I) or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated cytokine production by such mammal's cell, such as but not

limited to monocytes and/or macrophages.

[0086] Compounds of Formula (I) or (II) are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF and are therefore of use in therapy. IL-1, IL-6, IL-8 and TNF affect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these pro-inflammatory cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

[0087] Described herein is a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering amount of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof.

[0088] In particular, compounds of Formula (I) or a pharmaceutically acceptable salt thereof are of use in the prophylaxis or therapy of any disease state in a human, or other mammal, which is exacerbated by or caused by excessive or unregulated IL-1, IL-8 or TNF production by such mammal's cell, such as, but not limited to, monocytes and/or macrophages.

[0089] Also described herein is thacompounds of Formula (I) are capable of inhibiting inducible proinflammatory proteins, such as COX-2, also referred to by many other names such as prostaglandin endoperoxide synthase-2 (PGHS-2) and are therefore of use in therapy. These proinflammatory lipid mediators of the cyclooxygenase (CO) pathway are produced by the inducible COX-2 enzyme. Regulation, therefore of COX-2 which is responsible for the these products derived from arachidonic acid, such as prostaglandins affect a wide variety of cells and tissues are important and critical inflammatory mediators of a wide variety of disease states and conditions. Expression of COX-1 is not effected by compounds of Formula (I). This selective inhibition of COX-2 may alleviate or spare ulcerogenic liability associated with inhibition of COX-1 thereby inhibiting prostoglandins essential for cytoprotective effects. Thus inhibition of these pro-inflammatory mediators is of benefit in controlling, reducing and alleviating many of these disease states. Most notably these inflammatory mediators, in particular prostaglandins, have been implicated in pain, such as in the sensitization of pain receptors, or edema. This aspect of pain management therefore includes treatment of neuromuscular pain, headache, cancer pain, and arthritis pain. Compounds of Formula (I) or a pharmaceutically acceptable salt thereof, are of use in the prophylaxis or therapy in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

[0090] Described herein is a method of inhibiting the synthesis of COX-2 which comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The present application also describes a method of prophylaxis treatment in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

[0091] A method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof is also described.

[0092] There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, stroke, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic β cells and Alzheimer's disease.

[0093] In a further aspect, this application describes a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0094] Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

[0095] Compounds of Formula (I) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibiting-compounds of Formula (I). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex. Accordingly, in a further aspect, this invention relates to a method of treating a mammal afflicted with a human immunodeficiency virus (HIV) which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof.

[0096] Compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retrovirus infections, such as but not limited to feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

[0097] The compounds of Formula (I) may also be used topically in the treatment or prophylaxis of topical disease states mediated by or exacerbated by excessive cytokine production, such as by IL-1 or TNF respectively, such as inflamed joints, eczema, psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

[0098] Compounds of Formula (I) have also been shown to inhibit the production of IL-8 (Interleukin-8, NAP). Accordingly, in a further aspect, this invention relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0099] There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases are characterized by massive neutrophil infiltration such as, psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. All of these diseases are associated with increased IL-8 production which is responsible for the chemotaxis of neutrophils into the inflammatory site. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8 has the unique property of promoting neutrophil chemotaxis and activation. Therefore, the inhibition of IL-8 production would lead to a direct reduction in the neutrophil infiltration.

[0100] The compounds of Formula (I) are administered in an amount sufficient to inhibit cytokine, in particular IL-1, IL-6, IL-8 or TNF, production such that it is regulated down to normal levels, or in some case to subnormal levels, so as to ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-6, IL-8 or TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL-6, IL-8 or TNF greater than or equal to 1 picogram per ml; (ii) any cell associated IL-1, IL-6, IL-8 or TNF; or (iii) the presence of IL-1, IL-6, IL-8 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-6, IL-8 or TNF, respectively, is produced.

[0101] The discovery that the compounds of Formula (I) are inhibitors of cytokines, specifically IL-1, IL-6, IL-8 and TNF is based upon the effects of the compounds of Formulas (I) on the production of the IL-1, IL-8 and TNF in *in vitro* assays which are described herein.

[0102] As used herein, the term "inhibiting the production of IL-1 (IL-6, IL-8 or TNF)" refers to:

a) a decrease of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the cytokine by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the genomic level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels;

c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-6, IL-8 or TNF) as a postranslational event; or

d) a down regulation, at the translational level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels.

[0103] As used herein, the term "TNF mediated disease or disease state" refers to any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease stated mediated by TNF.

[0104] As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epideral keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF-α) and Tumor Necrosis Factor beta (TNF-β).

[0105] As used herein, the term "cytokine interfering" or "cytokine suppressive amount" refers to an effective amount of a compound of Formula (I) or (II) which will cause a decrease in the *in vivo* levels of the cytokine to normal or sub-

normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

[0106] As used herein, the cytokine referred to in the phrase "inhibition of a cytokine, for use in the treatment of a HIV-infected human" is a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

[0107] As TNF-β (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-a and TNF-β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

[0108] A new member of the MAP kinase family, alternatively termed CSBP, p38, or RK, has been identified independently by several laboratories recently. Activation of this novel protein kinase via dual phosphorylation has been observed in different cell systems upon stimulation by a wide spectrum of stimuli, such as physicochemical stress and treatment with lipopolysaccharide or proinflammatory cytokines such as interleukin-1 and tumor necrosis factor. The cytokine biosynthesis inhibitors, of the present invention, compounds of Formula (I), (II) and (A), have been determined to be potent and selective inhibitors of CSBP/p38/RK kinase activity. These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In particular, for the first time a definitive signal transduction pathway can be prescribed to the action of lipopolysaccharide in cytokine production in macrophages.

[0109] The cytokine inhibitors were subsequently tested in a number of animal models for anti-inflammatory activity. Model systems were chosen that were relatively insensitive to cyclooxygenase inhibitors in order to reveal the unique activities of cytokine suppressive agents. The inhibitors exhibited significant activity in many such in vivo studies. Most notable are its effectiveness in the collagen-induced arthritis model and inhibition of TNF production in the endotoxic shock model. In the latter study, the reduction in plasma level of TNF correlated with survival and protection from endotoxic shock related mortality. Also of great importance are the compounds effectiveness in inhibiting bone resorption in a rat fetal long bone organ culture system. Griswold et al., (1988) *Arthritis Rheum.* **31**:1406-1412; Badger, et al., (1989) *Circ. Shock* **27**, 51-61; Votta et al., (1994)*in vitro. Bone* **15**, 533-538; Leeet al., (1993). B *Ann. N. Y. Acad. Sci.* **696**, 149-170.

[0110] In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be Formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent Compounds of Formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in conventional dosage forms prepared by combining a compound of Formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the Formulation and not deleterious to the recipient thereof.

[0111] The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

[0112] A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

[0113] Compounds of Formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula (I) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

[0114] Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the Formulation. It may however comprise as much as

10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the Formulation.

[0115] Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

[0116] Creams, ointments or pastes according to the present invention are semi-solid Formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The Formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

[0117] Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

[0118] Compounds of formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of Formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol Formulation or a metered dose inhaler, may be prepared by conventional techniques.

[0119] For all methods of use disclosed herein for the compounds of Formula (I), the daily oral dosage regimen will preferably be from about 0.01 to about 30 mg/kg of total body weight, preferably from about 0.01 to 10 mg/kg, more preferably from about 0.01 mg to 5mg. The daily parenteral dosage regimen about 0.001 to about 30 mg/kg of total body weight, preferably from about 0.01 to about 10 mg/kg, and more preferably from about 0.01 mg to 5mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharma-ceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

BIOLOGICAL EXAMPLES

[0120] The cytokine-inhibiting effects of compounds of the present invention were determined by the following *in vitro* assays:

Interleukin -1 (IL-1) : Human peripheral blood monocytes were isolated and purified from either fresh blood preparations from volunteer donors, or from blood bank buffy coats, according to the procedure of Colotta *et al*, J Immunol, **132**, 936 (1984). These monocytes (1x106) were plated in 24-well plates at a concentration of 1-2 million/ml per well. The cells were allowed to adhere for 2 hours, after which time non-adherent cells were removed by gentle washing. Test compounds were then added to the cells for 1h before the addition of lipopolysaccharide (50 ng/ml), and the cultures were incubated at 37°C for an additional 24h. At the end of this period, culture supernatants were removed and clarified of cells and all debris. Culture supernatants were then immediately assayed for IL-1 biological activity, either by the method of Simon *et al.*, J. Immunol. Methods, **84**, 85, (1985) (based on ability of IL-1 to stimulate a Interleukin 2 producing cell line (EL-4) to secrete IL-2, in concert with A23187 ionophore)

or the method of Lee *et al.*, J. ImmunoTherapy, **6** (1), 1-12 (1990) (ELISA assay). The compounds of Formula (I), as evidenced by Examples 1 to 24 were shown to be inhibitors of *in vitro* IL-1 produced by human monocytes.

Tumour Necrosis Factor (TNF): Human peripheral blood monocytes were isolated and purified from either blood bank buffy coats or plateletpheresis residues, according to the procedure of Colotta, R. *et al.*, J Immunol, **132**(2), 936 (1984). The monocytes were plated at a density of 1x106 cells/ml medium/well in 24-well multi-dishes. The cells were allowed to adhere for 1 hour after which time the supernatant was aspirated and fresh medium (1ml, RPMI-1640, Whitaker Biomedical Products, Whitaker, CA) containing 1% fetal calf serum plus penicillin and streptomycin (10 units/ml) added. The cells were incubated for 45 minutes in the presence or absence of a test compound at 1nM-10mM dose ranges (compounds were solubilized in dimethyl sulfoxide/ethanol, such that the final solvent concentration in the culture medium was 0.5% dimethyl sulfoxide/0.5% ethanol). Bacterial lipopoly-saccharide (*E. coli* 055:B5 [LPS] from Sigma Chemicals Co.) was then added (100 ng/ml in 10 ml phosphate buffered saline) and cultures incubated for 16-18 hours at 37°C in a 5% CO2 incubator. At the end of the incubation period, culture supernatants were removed from the cells, centrifuged at 3000 rpm to remove cell debris. The supernatant was then assayed for TNF activity using either a radio-immuno or an ELISA assay, as described in WO 92/10190 and by Becker *et al.*, J Immunol, 1991, **147**, 4307. The compounds of Formula (I), as evidenced by Examples 1 to 24 were shown to be inhibitors of *in vitro* TNF produced by human monocytes.

IL-1 and TNF inhibitory activity does not seem to correlate with the property of the compounds of Formula (I) in mediating arachidonic acid metabolism inhibition. Further the ability to inhibit production of prostaglandin and/or leukotriene synthesis, by nonsteroidal anti-inflammatory drugs with potent cyclooxygenase and/or lipoxygenase inhibitory activity does not mean that the compound will necessarily also inhibit TNF or IL-1 production, at non-toxic doses.

Interleukin -8 (IL-8): Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) are maintained in culture medium supplemented with 15% fetal bovine serum and 1% CS-HBGF consisting of aFGF and heparin. The cells are then diluted 20-fold before being plated (250µl) into gelating coated 96-well plates. Prior to use, culture medium are replaced with fresh medium (200µl). Buffer or test compound (25µl, at concentrations between 1 and 10µM) is then added to each well in quadruplicate wells and the plates incubated for 6h in a humidified incubator at 37°C in an atmosphere of 5% CO2. At the end of the incubation period, supernatant is removed and assayed for IL-8 concentration using an IL-8 ELISA kit obtained from R&D Systems (Minneapolis, MN). All data is presented as mean value (ng/ml) of multiple samples based on the standard curve. IC50's where appropriate are generated by non-linear regression analysis.

Cytokine Specific Binding Protein Assay

[0121] A radiocompetitive binding assay was developed to provide a highly reproducible primary screen for structure-activity studies. This assay provides many advantages over the conventional bioassays which utilize freshly isolated human monocytes as a source of cytokines and ELISA assays to quantify them. Besides being a much more facile assay, the binding assay has been extensively validated to highly correlate with the results of the bioassay. A specific and reproducible cytokine inhibitor binding assay was developed using soluble cystosolic fraction from THP.1 cells and a radiolabeled compound. Patent Application USSN 08/123175 Lee et al., filed September 1993, USSN; Lee et al., PCT 94/10529 filed 16 September 1994 and Lee et al., *Nature* 300, n(**72**), 739-746 (Dec. 1994) whose disclosures are incorporated by reference herein in its entirety describes the above noted method for screening drugs to identify compounds which interact with and bind to the cytokine specific binding protein (hereinafter CSBP). However, for purposes herein the binding protein may be in isolated form in solution, or in immobilized form, or may be genetically engineered to be expressed on the surface of recombinant host cells such as in phage display system or as fusion proteins. Alternatively, whole cells or cytosolic fractions comprising the CSBP may be employed in the creening protocol. Regardless of the form of the binding protein, a plurality of compounds are contacted with the binding protein under conditions sufficient to form a compound/ binding protein complex and compound capable of forming, enhancing or interfering with said complexes are detected.

[0122] Representative final compounds of Formula (I), Examples 3 to 27 all demonstrated positive inhibitory activity, such as from a binding IC50 of about 0.18 to 5 micromolar, in this binding assay, except for Example 12 which compound was not tested.

Prostoglandin endoperoxide synthase-2 (PGHS-2) assay:

[0123] The following assay describes a method for determining the inhibitory effects of compounds of Formula (I) on human PGHS-2 protein expression in LPS stimulated human monocytes.

Method: Human peripheal blood monocytes were isolated from buffy coats by centrifugation through Ficoll and Percoll gradients. Cells were seeded at 2 X 106/well in 24 well plates and allowed to adhere for 1 hour in RPMI supplemented with 1% human AB serum, 20mM L-glutamine, Penicillin-Streptomycin and 10mM HEPES. Compounds were added at various concentrations and incubated at 37°C for 10 minutes. LPS was added at 50 ng/well (to induce enzyme expression) and incubated overnight at 37°C. The supernatant was removed and cells washed once in cold PBS. The cells were lysed in 100μl of cold lysis buffer(50mM Tris/HCl pH 7.5, 150mM NaCl, 1% NP40, 0.5% sodium deoxycholate, 0.1% SDS, 300ug/ml DNAse, 0.1% TRITON X-100, 1mM PMSF, 1mM leupeptin, 1mM pepstatin). The lysate was centrifuged (10,000 X g for 10 min. at 4°C) to remove debris and the soluble fraction was subjected to SDS PAGE. analysis (12% gel). Protein separated on the gel were transferred onto nitrocellulose membrane by electrophoretic means for 2 hours at 60 volts. The membrane was pretreated for one hour in PBS/0.1% Tween 20 with 5% non-fat dry milk. After washing 3 times in PBS/Tween buffer, the membrane was incubated with a 1:2000 dilution of a monospecific antiserum to PGHS-2 or a 1:1000 dilution of an antiserum to PGHs-1 in PBS/Tween with 1% BSA for one hour with continuous shaking. The membrane was washed 3X in PBS/Tween and then incubated with a 1:3000 dilution of horseradish peroxidase conjugated donkey antiserum to rabbit Ig (Amersham) in PBS/Tween with 1% BSA for one hour with continuous shaking. The membrane was then washed 3X in PBS/Tween and the ECL immunodetection system (Amersham) was used to detect the level of expression of prostaglandin endoperoxide synthases-2.

[0124] RESULTS: The following compounds were tested and found to be active (inhibited LPS induced PGHS-2 protein expression in rank order potency similar to that for inhibiting cytokine production as noted in assays indicated):

1-[3-(4-Morpholinyl)propyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, a representative compound of Formula (I);
4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole
6-(4-Fluorophenyl)-2,3-dihydro-5-(4-pyridinyl)imidazo[2,1-b]thiazole; Dexamethasone

[0125] Several compounds were tested and found to be inactive (up to 10uM): 2-(4-Methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-(5H)-pyrrolo[1,2-a]imidazole rolipram ; phenidone and NDGA. None of the compounds tested was found to inhibit PGHS-1 or cPLA2 protein levels in similar experiments.

SYNTHETIC EXAMPLES

[0126] All temperatures are given in degrees centigrade, all solvents are highest available purity and all reactions run under anydrous conditions in an argon atmosphere unless otherwise indicated.

[0127] In the Examples, all temperatures are in degrees Centigrade (°C). Mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated. 1H-NMR (hereinafter "NMR") spectra were recorded at 250 MHz using a Bruker AM 250 or Am 400 spectrometer. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant. Flash chromatography is run over Merck Silica gel 60 (230 - 400 mesh).

Reference Example 1

1-[3-(4-Morpholinyl)propyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole

[0128]

a) 4-fluorophenyl-tolylthiomethylformamide: A solution of p-fluorobenzaldehyde (13.1 milliliters (hereinafter mL), 122 millimoles (hereinafter mmol) thiocresol (16.64 grams (hereinafter g), 122 mmol), formamide (15.0 mL, 445 mmol), and toluene (300 mL) were combined and heated to toluene reflux with azeotropic removal of H2O for 18 h. The cooled reaction was diluted with EtOAc (500 mL) and washed with satd aq Na2CO3(3 x 100 mL), satd aq NaCl (100 mL), dried (Na2SO4), and concentrated. The residue was triturated with petroleum ether, filtered and dried in vacuo to afford 28.50 g of the title compound as a white solid (85 %). melting point (hereinafter mp) = 119 - 120°.

b) 4-fluorophenyl-tolylthiomethylisocyanide: The compound of example 1(a) (25 g, 91 mmol) in CH2Cl2 (300 mL) was cooled to -30° and with mechanical stirring POCl3 (11 mL, 110 mmol) was added dropwise followed by the dropwise addition of Et3N (45 mL, 320 mmol) with the temperature maintained below -30°. Stirred at -30° for 30 min and 5° for 2 h, diluted with CH2Cl2 (300 mL) and washed with 5% aq Na2CO3 (3 x 100 mL), dried (Na2SO4) and concentrated to 500 mL. This solution was filtered through a 12 x 16 cm cylinder of silica in a large sintered glass funnel with CH2Cl2 to afford 12.5 g (53%) of purified isonitrile as a light brown, waxy solid. IR (CH2Cl2) 2130 cm-1.

c) Pyridine-4-carboxaldehyde [4-Morpholinylprop-3-yl]imine: Pyridine-4-carboxaldehyde (2.14 g, 20 mmoL), 4-(3-aminopropyl)morpholine (2.88 g, 20 mmol), toluene (50 mL) and MgSO4 (2 g) were combined and stirred under argon for 18 h. The MgSO4 was filtered off and the filtrate was concentrated and the residue was reconcentrated from CH2C12 to afford 4.52 g (97%) of the title compound as a yellow oil containing less than 5% of aldehyde based on 1H NMR. 1H NMR (CD3Cl): d 8.69 (d, J = 4.5 Hz, 2H), 8.28 (s, 1H), 7.58 (d, J = 4.5 Hz, 2H), 3.84 (m, 6H), 2.44 (m, 6H), 1.91 (m, 2H).

d) 1-[3-(4-Morpholinyl)propyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole The compound of example 1(b) (1.41 g, 5.5 mmol), and the compound of example 1(c) (1.17 g, 5.0 mmol) and CH2Cl2 (10 mL) were cooled to 5°C. 1.5.7-triazabicyclo-[4.4.0]dec-5-ene, henceforth referred to as TBD, (0.71 g 5.0 mmol) was added and the reaction was kept at 5°C for 16 h, diluted with EtOAc (80 mL) and washed with satd aq Na2CO3 (2 x 15 mL). The EtOAc was extracted with 1 N HCl (3 x 15 mL), and the acid phases were washed with EtOAc (2 x 25 mL), layered with EtOAc (25 mL) and made basic by the addition of solid K2CO3 til pH 8.0 and then 10% NaOH til pH 10. The phases were separated and the aq was extracted with additional EtOAc (3 x 25 mL). The extracts were dried (K2CO3) concentrated and the residue was crystalized from acetone/hexane to afford 0.94 g (51%) of the title compound. mp = 149 - 150°.

Reference Example 10

a) α-(p-Toluenesulfonyl)-4-fluorobenzylformamide

[0129] To a stirred solution of 4-fluorobenzaldehyde (124g, 979mmoles) in acetonitrile (620mL, 5volumes) and toluene (620mL, 5volumes) was added formamide (110g, 2.45moles, 2.5equiv.) followed by chlorotrimethylsilane (119g, 1.07moles, 1.1equiv.). The reaction was heated at 50°C under nitrogen for 5hours. To the resulting white slurry was added p-toluenesulfinic acid (230g, 1.47moles, 1.5equiv.) and the reaction was heated at 50°C for an additional 5hours then cooled to ambient temperature. Methanol (250mL) and t-butyl methyl ether (620mL) were added. After 15minutes the reaction was poured into water (3L) pre-cooled to 0°C. After stirring for 30minutes at 0°C, the product was collected by suction filtration and rinsed with t-butyl methyl ether (250mL). The product, a white, crystalline solid, was dried to a constant weight at 40°C/<1mm Hg to afford 270g (879mmoles) of desired product (90% yield).
1H NMR (300 MHz, CD3CN) δ 7.99 (1H, s), 7.92 (1H, m), 7.71 (2H, d, J = 8.3 Hz), 7.49 (2H, dd, J = 5.3, 8.8 Hz), 7.39 (2H, d, J = 8.1 Hz), 7.16 (2H, t, J = 8.8 Hz), 6.31 (1H, d, J = 10.6 Hz), 2.42 (3H, s).

[0130] Alternative conditions to those used above in part (a) were employed:

a) toluene at about 50°C; b) acetonitrile at about 50°C; c) and using the conditions above but at temperatures of 30, 40, 50, 60 and 70°C.

b) α-(p-Toluenesulfonyl)-4-fluorobenzylisonitrile

[0131] A stirred suspension of α-(p-toluenesulfonyl)-4-fluorobenzylformamide produced in step (a) above, (100g, 325mmoles) in THF (650mL, 6.5volumes) was cooled to 0°C and POCl3 (46mL, 487mmoles, 1.5equiv.) was added. A 1°C exotherm was observed. After 15minutes at 0°C, the white slurry was cooled to -5°C. Triethylamine (166g, 1.62moles, 5equiv.) was added dropwise to the slurry over 45 minutes at such a rate to keep the reaction temperature below 0°C but above -5°C. Caution should be exercised at the beginning of the addition because the reaction has a tendency to exotherm quickly. After complete addition, the yellow slurry was stirred for 30minutes at 0°C. The reaction slurry has a tendency to darken during the stirring period. The reaction was poured into a mixture of saturated aqueous sodium bicarbonate (1L) and ethyl acetate (1L), both pre-cooled to 0°C. The organic phase was subsequently washed with water followed by brine. The organic phase was concentrated under vacuum via rotary evaporation until about 10% of the initial volume remained. 1-Propanol (200mL) was added and concentrated again under vacuum at 35°C until about 10% of the initial volume remained. This process was repeated with fresh 1-propanol (200mL). A fine, yellow precipitate was observed. The precipitate was cooled to 0°C and the product was collected by suction filtration and rinsed with 1-propanol (50mL). The off-white solid was dried to a constant weight at 40°C/<1mm to give 65.7g (227mmoles) of desired product, affording a 70% yield. 1H NMR (300 MHz, CDCl3) δ 7.62 (2H, d, J = 6.7 Hz), 7.46 (4H, m), 7.08 (2H, t, J = 8.6 Hz), 5.62 (1H, s), 2.46 (3H, s).

[0132] Alternative conditions to those used above in part (b) were employed, such as: a) different solvents: DME, DME/acetonitrile(10:1) using the same reaction conditions; b) using the reaction conditions above but ranging the temperature from -30, -15, -10, and 0°C; c) using reaction temperature at 0°C, and at -10°C; d) a variety of dehydrating agents including trifluroacetic anhydride, thionyl chloride, and oxalyl chloride.

Reference Example 11

5-(2-Acetamido-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole

[0133] To a solution of the 2-acetylamido pyrimidinyl-4-carboxaldehyde (0.84 g, 5.08 mmol) and 1-methylpiperidin-4-yl-amino dihydrochloride salt (1.04 g, 5.59 mmol) in 21 mL of DMF was added powdered K2CO3 (1.54 g, 11.2 mmol). After approx 6 h, the $\underline{\alpha}$-(p-Toluenesulfonyl)-4-fluorobenzylisonitrile, produced in step (b) Example 10 above, (1.76 g, 6.10 mmol) and powdered K2CO3 (0.84 g, 6.10 mmo) were added and the sides of the flask rinsed with 5 mL of DMF. After 16 h, 300 mL of H2O were added to the reaction mixture and the solution was extracted with EtOAc (3 X 100 mL). The combined organics were washed with H2O (3 X 50 mL), dried over Na2SO4 and concentrated. The pure title compound (0.75 g, 38%) was recrystallized from EtOAc as a pale yellow crystal. 1H NMR (300 MHz, CDCl3) δ 8.71 (1H, s), 8.39 (1H, d, J= 5.2 Hz), 7.81 (1H, s), 7.39 (2H, m), 7.13 (2H, t, J = 8.7 Hz), 6.81 (1H, d, J = 5.2 Hz), 4.88 (1H, m), 2.94 (2H, d, J = 10.1 Hz), 2.47 (3H, s), 2.32 (3H, s), 2.07 (6H, m).

Example 23

5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl) imidazole

a) Pyridine-4-carboxaldehyde(ethyl 4-amino-piperdinecarboxylate)imine

[0134] Following the procedure of example 1(c) herein, except substituting ethyl 4-amino-piperdinecarboxylate for 4-(3-aminopropyl)morpholine afforded the title compound in quantitative yield.

b) 1-[(1-Ethoxycarbonyl)piperdin-4-yl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole

[0135] Following the procedure of example 1(d) except substituting pyridine-4-carboxaldehyde(ethyl 4-amino-piperdinecarboxylate)imine for pyridine-4-carboxaldehyde [4-morpholinylprop-3-yl]imine afforded the title compound as a light yellow solid in 71% yield.

c) 4-(4-Fluorophenyl)-5-(4-pyridyl)-1-(4-piperdinyl)imidazole

[0136] Concentrated hydrochloric acid (40 mL) was added to 1-[(1-ethoxycarbonyl)-piperdin-4-yl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole (9.4 g, 24 mmol) and the mixture was heated to reflux for 18 h. The resulting yellow solution was cooled to ambient temperature and neutralized with 10% aqueous sodium hydroxide. The precipitate was collected, washed with water and air-dried to afford the title compound as a white solid in 71% yield. ESMS = 323 [M+H]; m.p. 185-187.0°C.

[0137] The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

Claims

1. 5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole, or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising 5-(4-pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

3. The use of 5-(4-pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating inflammation.

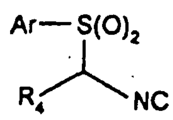
4. The use of 5-(4-pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a CSBP/RK/p38 kinase mediated disease.

5. The use according to claim 4 in which the CSBP/RK/p38 kinase mediated disease is selected from the group consisting of:

   a) rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, acute synovitis, gouty arthritis and other arthritic conditions;
   b) sepsis, septic shock, endotoxic shock, gram negative sepsis and toxic shock syndrome;

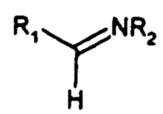
c) asthma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis and pulmonary sarcososis;
d) bone resorption diseases, osteoporosis, graft vs. host reaction, allograft rejections and pyresis;
e) stroke, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis and cerebral malaria;
f) diabetes and pancreatic β-cells;
g) multiple sclerosis and muscle degeneration;
h) atherosclerosis and Alzheimer's disease;
i) eczema, psoriasis, sunburn and conjunctivitis; and
j) Crohn's disease, ulcerative colitis and inflammatory bowel disease.

6. A process for the production of a compound according to claim 1 which comprises reacting a compound of formula (IIa):



(IIa)

with a compound of formula (III):



(III)

and a base strong enough to deprotonate the isonitrile moiety of formula (IIa); and wherein the imine of formula (III) is formed in situ prior to reaction with the compound of formula (IIa); R_1 is 4-pyridyl or a precursor thereof, R_2 is 4-piperidinyl or a precursor thereof, R_4 is 4-fluorophenyl or a precursor thereof, and Ar is an optionally substituted phenyl group, and thereafter if necessary, converting a precursor of R_1, R_2 or R_4 to a group R_1, R_2 or R_4.

7. The process according to claim 6 wherein the base is an amine, an amide, a carbonate, a hydride, or an alkyl or aryl lithium reagent or a mono-, di- or tribasic phosphate.

8. The process according to claim 6 or 7 wherein the imine is formed in situ: a) by reacting an aldehyde of the formula R_1CHO, wherein R_1 is 4-pyridyl, with a primary amine of formula R_2NH_2 wherein R_2 is 1-t-butoxycarbonyl-4-piperidinyl or 4-piperidinyl and R_2 may be suitably protected as necessary.

9. The process according to claim 8 wherein formation of the imine in situ utilises dehydrating conditions.

10. The process according to any one of claims 6 to 9 which is further performed in a solvent selected from N,N-dimethylformamide (DMF), a halogenated solvent, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), an alcohol, benzene, toluene, and DME.

11. The process according to claim 8 wherein:

a) the aldehyde of formula R_1CHO is formed in situ, or
b) the aldehyde is formed by the hydrolysis of an acetal of the formula $R_1CH(OR_a)_2$ wherein R_1 is 4-pyridyl or a precursor thereof, and R_a is C_{1-6}alkyl, aryl, aryl C_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl.

12. 5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(1-t-butoxycarbonyl-4-piperidinyl)imidazole, or a pharmaceutically acceptable salt thereof.

13. 5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(1-t-butoxycarbonyl-4-piperidinyl)imidazale.

14. 5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole.

15. A pharmaceutical composition comprising 5-(4-pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole and a pharmaceutically acceptable carrier or diluent.

Patentansprüche

1. 5-(4-Pyridyl)-4-(4-fluorphenyl)-1-(4-piperidinyl)imidazol oder ein pharmazeutisch verträgliches Salz davon.

2. Arzneimittel, umfassend 5-(4-Pyridyl)-4-(4-fluorphenyl)-1-(4-piperidinyl)imidazol oder ein pharmazeutisch verträgliches Salz davon und einen pharmazeutisch verträglichen Träger oder ein pharmazeutisch verträgliches Verdünnungsmittel.

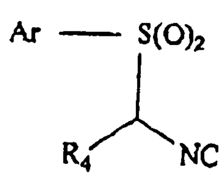
3. Verwendung von 5-(4-Pyridyl)-4-(4-fluorphenyl)-1-(4-piperidinyl)imidazol oder eines pharmazeutisch verträglichen Salzes davon zur Herstellung eines Medikaments zur Behandlung von Entzündungen.

4. Verwendung von 5-(4-Pyridyl)-4-(4-fluorphenyl)-1-(4-piperidinyl)imidazol oder eines pharmazeutisch verträglichen Salzes davon zur Herstellung eines Medikaments zur Behandlung einer CSBP/RK/p38-Kinase vermittelten Erkrankung.

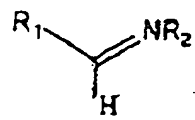
5. Verwendung gemäß Anspruch 4, wobei die CSBP/RK/p38-Kinase vermittelte Erkrankung ausgewählt ist aus:

   a) rheumatoider Arthritis, rheumatoider Spondylitis, Osteoarthritis, psoriatische Arthritis, traumatischer Arthritis, durch Röteln hervorgerufener Arthritis, akuter Synovialitis, Gichtarthritis und anderen arthritischen Zuständen;
   b) Sepsis, septischem Schock, endotoxischem Schock, gram-negativer Sepsis und toxischem Schocksyndrom;
   c) Asthma, adult respiratory distress syndrome, chronischer Lungenentzündung, Silikose und Lungensarkoidose;
   d) Knochenresorptionerkrankungen, Osteoporose, Transplantat-Wirt-Reaktion, Allotransplantatabstoßungen und Fieber;
   e) Schlaganfall, Herz- und Nierenreperfusionsschädigung, Thrombose, Glomerulonephritis und Malaria cerebralis;
   f) Diabetes und Pankreas-β-Zellen;
   g) Multiple Sklerose und Muskeldegeneration;
   h) Atherosklerose und Alzheimer Krankheit;
   i) Ekzem, Psoriasis, Sonnenbrand und Bindehautentzündung; und
   j) Morbus Crohn, Colitis ulcerosa und entzündlicher Darmerkrankung.

6. Verfahren zur Herstellung einer Verbindung gemäß Anspruch 1, welches Umsetzen einer Verbindung der Formel (IIa):



mit einer Verbindung der Fomlel (III):



und einer Base, die stark genug ist, um die Isonitrileinheit der Formel (IIa) zu deprotonieren; und wobei das Imin der Formel (III) vor der Umsetzung mit der Verbindung der Formel (IIa) in situ gebildet wird; R_1 eine 4-Pyridylgruppe oder eine Vorstufe davon ist, R_2 eine 4-Piperidinylgruppe oder eine Vorstufe davon ist, R_4 eine 4-Fluorphenylgruppe oder eine Vorstufe davon ist und Ar eine gegebenenfalls substituierte Phenylgruppe ist, und anschließend, falls notwendig, Umsetzen einer Vorstufe von R_1, R_2 oder R_4 zu einer Gruppe R_1, R_2 oder R_4 umfasst.

7. Verfahren gemäß Anspruch 6, wobei die Base ein Amin, ein Amid, ein Carbonat, ein Hydrid oder ein Alkyl- oder Aryllithiumreagens oder ein ein-, zwei- oder dreibasiges Phosphat ist.

8. Verfahren gemäß Anspruch 6 oder 7, wobei das Imin in situ durch Umsetzen eines Aldehyds der Formel R_1CHO, wobei R_1 eine 4-Pyridylgruppe ist, mit einem primären Amin der Formel R_2NH_2, wobei R_2 eine 1-t-Butoxycarbonyl-4-piperidinylgruppe oder eine 4-Piperidinylgruppe ist und R_2 nötigenfalls auf geeignete Weise geschützt sein kann, gebildet wird.

9. Verfahren gemäß Anspruch 8, wobei die in situ Bildung des Imins unter dehydratisierenden Bedingungen erfolgt.

10. Verfahren gemäß einem der Ansprüche 6 bis 9, das ferner in einem Lösungsmittel durchgeführt wird, das ausgewählt ist aus N,N-Dimethylformamid (DMF), einem halogenierten Lösungsmittel, Tetrahydrofuran (THF), Dimethylsulfoxid (DMSO), einem Alkohol, Benzol, Toluol und DME.

11. Verfahren gemäß Anspruch 8, wobei:

   a) der Aldehyd der Formel R_1 CHO in situ gebildet wird oder
   b) der Aldehyd durch Hydrolyse eines Acetals der Formel $R_1CH(OR_3)_2$ gebildet wird, wobei R_1 eine 4-Pyridylgruppe oder eine Vorstufe davon ist und R_a ein C_{1-6}-Alkyl-, Aryl-, Aryl-C_{1-6}-alkyl-, Heteroaryl- oder Heteroaryl-C_{1-6}-alkylrest ist.

12. 5-(4-Pyridyl)-4-(4-fluorphenyl)-1-(1-t-butoxycarbonyl-4-piperidinyl)imidazol oder ein pharmazeutisch verträgliches Salz davon.

13. 5-(4-Pyridyl)-4-(4-fluorphenyl)-1-(1-t-butoxycarbonyl-4-piperidinyl)imidazol.

14. 5-(4-Pyridyl)-4-(4-fluorphenyl)-1-(4-piperidinyl)imidazol.

15. Arzneimittel, umfassend 5-(4-Pyridyl)-4-(4-fluorphenyl)-1-(4-piperidinyl)imidazol und einen pharmazeutisch verträglichen Träger oder ein pharmazeutisch verträgliches Verdünnungsmittel.

Revendications

1. 5-(4-pyridyl)-4-(4-fluorophényl)-1-(4-pipéridinyl)-imidazole, ou un de ses sels pharmaceutiquement acceptables.

2. Composition pharmaceutique comprenant du 5-(4-pyridyl)-4-(4-fluorophényl)-1-(4-pipéridinyl)imidazole, ou un de ses sels pharmaceutiquement acceptables, et un support ou diluant pharmaceutiquement acceptable.

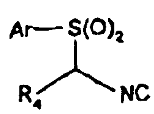
3. Utilisation du 5-(4-pyridyl)-4-(4-fluorophényl)-1-(4-pipéridinyl)imidazole ou d'un de ses sels pharmaceutiquement acceptables, dans la production d'un médicament destiné au traitement de l'inflammation.

4. Utilisation du 5-(4-pyridyl)-4-(4-fluorophényl)-1-(4-pipéridinyl)imidazole ou d'un de ses sels pharmaceutiquement acceptables, dans la production d'un médicament destiné au traitement d'une maladie à médiation par la kinase CSBP/RK/p38.

5. Utilisation suivant la revendication 4, dans laquelle la maladie à médiation par la kinase CSBP/RK/p38 est choisie dans le groupe consistant en :

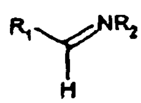
a) l'arthrite rhumatoïde, la spondylite rhumatoïde, l'osthéoarthrite, l'arthrite psoriasique, l'arthrite traumatique, l'arthrite provoquée par la rubéole, la synovite aiguë, l'arthrite goutteuse et d'autres états arthritiques ;
b) la septicémie, le choc septique, le choc endotoxique, la septicémie à bactéries Gram négatives et le syndrome de choc toxique ;
c) l'asthme, le syndrome de détresse respiratoire de l'adulte, une maladie inflammatoire pulmonaire chronique, la silicose et la sarcoïdose pulmonaire ;
d) des maladies de résorption du tissu osseux, l'ostéoporose, la réaction du greffon contre l'hôte, les rejets d'allogreffes et les états pyrétiques ;
e) un ictus, une lésion de reperfusion cardiaque, une lésion de reperfusion rénale, une thrombose, la glomérulonéphrite et le paludisme cérébral ;
f) le diabète et une affection des cellules β-pancréatiques ;
g) la sclérose en plaques et la dégénérescence musculaire;
h) l'athérosclérose et la maladie d'Alzheimer ;
i) l'eczéma, le psoriasis, les érythèmes solaires et la conjonctivite ;
et
j) la maladie de Crohn, la colite ulcérative et une maladie intestinale inflammatoire.

6. Procédé pour la production d'un composé suivant la revendication 1, qui comprend la réaction d'un composé de formule (IIa) :



(IIa)

avec un composé de formule (III) :



(III)

et une base suffisamment forte pour déprotoner le groupement isonitrile de la formule (IIa) ; et l'imine de formule (III) étant formée in situ avant la réaction avec le composé de formule (IIa) ; R_1 représente un groupe 4-pyridyle ou un de ses précurseurs, R_2 représente un groupe 4-pipéridinyle ou un de ses précurseurs, R_4 représente un groupe 4-fluorophényle ou un de ses précurseurs, et Ar représente un groupe phényle facultativement substitué, et ensuite, si nécessaire, la conversion d'un précurseur de R_1, R_2 ou R_4 en un groupe R_1, R_2 ou R_4.

7. Procédé suivant la revendication 6, dans lequel la base est une amine, un amide, un carbonate, un hydrure, ou un réactif du type alkyl- ou aryllithium ou un phosphate mono-, di- ou triacide.

8. Procédé suivant la revendication 6 ou 7, dans lequel l'imine est formée in situ : a) en faisant réagir un aldéhyde de formule R_1CHO, dans laquelle R_1 représente un groupe 4-pyridyle, avec une amine primaire de formule R_2NH_2 dans laquelle R_2 représente un groupe 1-tertiobutoxycarbonyl-4-pipéridinyle ou 4-pipéridinyle et R_2 peut être protégé convenablement de la manière nécessaire.

9. Procédé suivant la revendication 8, dans lequel la formation de l'imine in situ utilise des conditions de déshydratation.

10. Procédé suivant l'une quelconque des revendications 6 à 9, qui est en outre mis en oeuvre dans un solvant choisi entre le N-N-diméthylformamide (DMF), un solvant halogéné, le tétrahydrofuranne (THF), le diméthylsulfoxyde (DMSO), un alcool, le benzène, le toluène et le DME.

11. Procédé suivant la revendication 8, dans lequel :

    a) l'aldéhyde de formule R_1CHO est formé in situ, ou
    b) l'aldéhyde est formé par hydrolyse d'un acétal de formule $R_1CH(OR_a)_2$ dans laquelle R_1 représente un groupe 4-pyridyle ou un de ses précurseurs et R_a représente un groupe alkyle en C_1 à C_6, aryle, aryl(alkyle en C_1 à C_6), hétéroaryle ou hétéroaryl(alkyle en C_1 à C_6).

12. 5-(4-pyridyl)-4-(4-fluorophényl)-1-(1-tertio-butoxycarbonyl-4-pipéridinyl)imidazole, ou un de ses sels pharmaceutiquement acceptables.

13. 5-(4-pyridyl)-4-(4-fluorophényl)-1-(1-tertio-butoxycarbonyl-4-pipéridinyl)imidazole.

14. 5-(4-pyridyl)-4-(4-fluorophényl)-1-(4-pipéridinyl)-imidazole.

15. Composition pharmaceutique comprenant du 5-(4-pyridyl)-4-(4-fluorophényl)-1-(4-pipéridinyl)imidazole et un support ou diluant pharmaceutiquement acceptable.